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Research Paper

Breast conservation after neoadjuvant therapy for tumors ≥5 cm: A prospective cohort study

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ABSTRACT

Introduction: Neoadjuvant therapy (NT) can facilitate breast conservation (BC). Similar oncologic outcomes have been reported with BC and mastectomy for T1 and T2 lesions, but studies of BC results for tumors ≥5 cm are limited. Our experience with BC for tumors ≥5 cm is reported.

Patients and methods: A retrospective analysis of a prospectively collected database of all breast cancer patients treated with NT at our institution between 2003 and 2010 was performed to identify patients treated with BC for tumors ≥5 cm. Demographics, stage, tumor histology, pathologic response, tumor margins, failure patterns and rates, as well as survival rates were recorded.

Results: Thirty patients treated with BC after NT for large tumors were identified. The only selection criteria for BC were technical ability with acceptable cosmetic results and negative margins. Patients with genetic predisposition for additional breast cancer were excluded. The mean follow-up was 43 months and the mean age at diagnosis was 51. The mean tumor size at diagnosis was 6.4 cm and the mean pathological size was 2.1 cm. Four of thirty (13.3%) had either systemic progression or regional recurrence. Three patients had systemic progression, 2 had regional recurrence and none had local recurrence. At a mean follow-up of 43 months, the success rate of BC on intent to treat basis was 96.7%, with an overall survival of 86.7% and disease-free survival of 83.3%.

Conclusion: BC after NT is a safe option for carefully selected patients with tumors ≥5 cm. In this series, the oncologic results for the duration of the study were comparable to those reported after mastectomy.

1. Introduction

Multiple prospective randomized trials [1], some with a follow-up of 20 years, have established equivalent survival rates between breast conservation (BC) with negative margins and mastectomy. The EBCTCG meta-analysis [2] further demonstrated improved overall survival with the addition of radiation to surgery. Neoadjuvant therapy (NT) has become a common approach for management of locally advanced breast cancer. The theoretical advantage of this strategy is threefold: an earlier systemic therapy targeting micro metastases, the ability to assess tumor response in vivo and the possible downsizing of the tumor enabling BC.

The use of BC for larger tumors downsized by NT presents some concerns regarding the adequacy of the resection and the possibility of a piecemeal tumor response resulting in residual satellite nodules in the field of the original tumor. The data for T3 tumors are limited because such large tumor sizes at presentation are rare nowadays. In fact NSABP B-18 had only 13% of patients with T3 tumors [3] and NSABPB-27 had 29% of such patients [4]. Furthermore those patients are usually offered a mastectomy and little consideration is given to BC. In our institution we treat a relatively large percentage of patients presenting with locally advanced tumors. We sought to investigate the feasibility of BC in this very specific group of patients. The aim of this study was to report the survival rates and failure patterns for tumors ≥5 cm treated by BC after NT at our institution.

2. Patients and methods

After appropriate institutional IRB approval, a retrospective analysis of a prospectively collected database of all breast cancer patients treated with NT at our institution between 2003 and 2010 was performed to identify patients treated with BC for tumors ≥5 cm, not including T4 disease. All patients received NT, which consisted of either hormonal or chemotherapy treatments. At our institution patients with advanced locoregional and no systemic disease are usually offered NT; these include patients with tumors ≥5 cm. The decision for BC was made by the surgeon and the patient's preference,

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as well as surgical feasibility based on breast size, tumor location and residual tumor volume according to previously published principles [5]. A second attempt for breast conservation was done if positive margins were obtained, If not feasible completion mastectomy was performed. Advanced oncoplastic techniques and contralateral breast reduction were done when deemed necessary for cosmetic reasons. We refer to BC combined with bilateral breast reductions as an "oncoreductive procedure." Tumor size was assessed at presentation by mammography and ultrasound, and response to NT was characterized according to the RECIST criteria by measuring pathological size [6]. Tumor stage, histology grade, and receptor status were recorded and were available in the vast majority of the cases. Local, regional and systemic failure patterns were recorded during the follow-up interval. Qualitative and quantitative variables were analyzed by chi square and Student t test, respectively; $P < 0.05$ was considered significant. The work has been reported in line with the STROBE criteria [7].

3. Results

Two hundred ninety patients received NT, of whom 84 had tumors ≥5 cm and were not classified as T4. Fifty-four patients were not offered breast conservation because of patient preference, genetic predisposition for breast cancer, or because of surgical and oncologic inability. Thirty patients treated with breast conservation after NT make up the main study group. The average follow-up interval was 43 months and the mean age at diagnosis was 51 years. Tumor histology was ductal in 24/30 (80%) patients and lobular in 6/30 (20%). NT consisted of chemotherapy for 25/30 (83.3%) patients (23/25 ductal and 2/24 lobular) and hormonal therapy for 5/30 (16.7%) patients (1/5 ductal and 4/5 lobular). The mean tumor size at diagnosis was 6.4 cm. Estrogen receptors (ER) were positive in 17/30 (56.7%) patients and Her2 was amplified in 10/30 (33.3%) patients. Low grade was found in 6 (20%) patients, intermediate grade in 11 patients (37%) and high grade in 13 (43%) patients. Twenty four had an axillary dissection, 5 had SLNB and in 1 patient no axillary staging was done due to old age at diagnosis.

Negative margins were obtained at the first attempt in 28 patients and on the second attempts in one patient. One patient underwent a completion mastectomy for grossly positive margins. Eight patients underwent an oncoreductive procedure. The mean pathological size at the time of resection was 2.1 cm, and 6/30 (20%) patients had pCR in the breast and lymph nodes. Thirteen out of thirty (43.3%) patients had a complete clinical response, 8/30 (26.7%) had partial response and 9/30 (30%) had stable disease. Table 1 summarizes the characteristics of the study group. Patients undergoing mastectomy had statistically larger tumors at presentation and lower rates of HER2 amplified tumors.

Postoperative treatment consisted of radiation therapy to all but one patient who did not receive therapy due to old age at diagnosis. Adjuvant hormonal therapy was given to all ER positive patients, and one patient discontinued therapy. All Her-2 positive patients received trastuzumab.

Overall, at 43 months of follow-up, the success rate of BC on intent to treat basis was 96.7%. The disease-free survival was 83.3% and the overall survival was 86.7%, with four patients dying during the follow-up interval, 3 from metastatic disease and one from unrelated causes. The fourth patient was diagnosed at the age of 91 and had no evidence of disease at the time of death.

Local, regional and systemic failures, as well as breast cancer mortality and overall mortality, were compared between the BC and the mastectomy groups and are summarized in Table 2. There were no statistically significant differences in any of those parameters. In the BC group, three patients (10%) developed systemic progression, of whom one had concomitant regional recurrence. An additional patient had isolated regional recurrence for a total of 2/30 (6.7%) regional recurrence. No in breast local failure occurred. All patients with systemic progression or recurrence did not reach complete response to NT. In more details, one patient with positive margins who was treated by completion mastectomy developed regional recurrence 18 months after diagnosis and died 10 months following regional recurrence. The second patient developed bone metastasis 32 months after diagnosis and died 18 months following the systemic progression. The third patient developed bone, liver and lung metastasis 44 months after diagnosis and died 6 months following the systemic progression. The fourth patient developed regional recurrence in the axilla 44 months after diagnosis and was treated with local excision.

In comparison 9/54 patients treated with mastectomy had systemic failure (16.7%), 2 with concurrent regional failures (3.7%), and there were no local failures.

Similarly, 9/54 (16.7%) patients in the mastectomy group died from all causes, of which 5 (9.3%) were breast cancer deaths.

Table 1
Clinical characteristics.

	Breast conservation	Mastectomy	P value
Age			
Mean	51.4	52.9	Not significant (NS)
<50	17 (57)	22 (41)	
≥50	13 (43)	32 (59)	
Histology			
Ductal	24 (80)	38 (70)	NS
Lobular	6 (20)	16 (20)	
No data	0	2	
ER positive	17 (57)	33 (63)	NS
Her2 positive	10 (33)	5 (4)	0.014
Grade			
I	6 (20)	6 (11)	NS
II	11 (37)	21 (39)	
III	13 (43)	27 (50)	
Clinical size			
Mean	6.4	7.2	0.027
NT			
Chemotherapy	25 (83)	51 (95)	NS
Hormonal	5 (17)	3 (5)	
Pathological size			
Mean	2.2	2.5	NS
Pathological nodal status[a]			
N0/N1	22 (76)	40 (74)	NS
N2/N3	7 (24)	14 (26)	
Response			
Complete response	13 (43)	18 (33)	NS
Partial response	8 (27)	19 (35)	
No response	9 (30)	17 (32)	

[a] In 1 patient no axillary staging was done due to old age at diagnosis.

Table 2
Failure pattern and outcome at mean follow-up of 43 months.

	Breast conservation	Mastectomy	P value
Failure pattern	n = 30	n = 54	
Systemic	3/30 (10)	9/54 (18.5)	NS
Regional	2/30 (6.7)	2/54 (5.5)	
Local	0	0	
Breast cancer-specific death	3/30 (10)	5/54 (9.3)	NS
Death	4/30 (13.3)	9/54 (16.7)	

4. Discussion

NT is increasingly used for locoregional advanced disease. With the adoption of complex oncoplastic techniques, including oncoreductive procedures, patients with larger residual tumors following NT are candidates for BC. Our aim was to study a very specific group of patients presenting with very large tumors of ≥5 cm. This

specific subgroup has been largely under-represented in previous studies [3,4]. Our study includes 83 patients with tumors ≥5 cm that were not T4 tumors, of which 30 (36%) had BCT.

There are three main aspects to the evaluation of BC after NT for patients who were not surgical candidates at all or were candidates for a mastectomy only prior to NT. The first aspect is the success rate of BC or the ability to perform the surgery and obtain a clear margin, which is influenced partly by the response to NT. The success rate ramifies into the immediate success rate and the long-term success rate in conserving the breast. The complete clinical response and pCR rates are not statistically higher than published by others [3]. As can be seen in our results the immediate success rate was 96.7%; these results are not inferior to previously published data where the positive margins rate may be as low as 12.4% [8], and the reported short-term completion mastectomy rate, 14% [9]. The overall 5-year local failure rates after BC and radiation vary between 6.7% for node negative disease and 11% for node positive disease [2].

The second aspect is the disease-free survival, disease-specific survival and the overall survival when compared to mastectomy patients with the same stage of disease at presentation. These rates are not inferior to the results of the patients undergoing mastectomy in our study.

Different from other publications we did not mandate shrinkage below a specific tumor size after NT or a specific histology in order to be eligible for BC. Our series included 6 patients with lobular carcinoma, 6 patients treated with hormonal NT and a mean ypT of 2.1 cm. Only the technical ability of breast conserving surgery with acceptable cosmetics and negative margins dictated the eligibility. That requirement does take into account also the breast size, tumor location and the glandular density, in addition to the residual tumor volume [5]. Response to therapy, however, still plays a role in the decision for BC, resulting in a selection bias when comparing our BC group to the mastectomy group.

The third and most important aspect is the local recurrence rate. Different studies have reported local recurrence rates with BC after NT; however, in most studies, the proportion of T3 tumors was small. Additionally the results are not easily comparable because of differences in criteria for NT and for breast conservation after treatment and because of inconsistencies in the reporting of receptor status. Furthermore in some studies the local recurrence rates are reported jointly for BCT and mastectomy. In Table 3 we have extrapolated the T3 relevant results from the different studies and added our own results for comparison.

Our study has a few limitations. First, it is a retrospective analysis of a prospectively collected database; second, an ideal comparison would have been with the subgroup of patients who were BC candidates but still elected mastectomy; however, this group was not identified separately.

Following is a short review of previously published data. Touboul et al. [10] reported a 20% 10-year local failure rate in 47 selected patients with residual tumors <3 cm following combination of NT and radiation that were treated with BC. In a series by Mauriac et al. [12], no preoperative radiation was given, and a different cutoff treatment was tailored according to the response to NT; NT was followed by radiation alone for complete responders, BC for residual tumors ≤2 cm and completion mastectomy for residual tumors > 2 cm. Forty patients underwent BC surgery, with a 23% local failure rate at 124 months of follow-up.

In the subgroup of patients who were downstaged to BC following NT in the NSABP 18 trial [3], the local failure rate was 7% in patients who were eligible for BC before therapy vs. 15% in those who were downstaged to BC by NT. In a study from Institute Curie [12], the reported rate of local failure was 16% and 21.5% at 5 and 10 years, respectively, and only 10% of patients had T3 disease.

A number of trials have reported a low local failure rate in BC following NT. In a study by Bonadonna et al. [11], patients eligible for mastectomy were treated by NT, and BC was performed in 63%, in which 11% were T3. The overall local failure rate was 6.8% and only 4.3% in the T3 subset. In a surgery outcome analysis of the NOAH trial [18], which was restricted to HER2 positive patients treated with chemotherapy and trastuzumab, no local failure was found in patients who underwent BC during a mean follow-up of 3.5 years. The rate of BC was low since BC was recommended mainly for tumors <4 cm at presentation or upon patient's request in larger tumors if an objective response to NT was achieved; only16% of tumors larger than 5 cm underwent BC. Five percent local failure rate was reported in the M.D. Anderson series of BC following NT [15], including all T stages and without specifics regarding eligibility for breast conservation prior to NT. In the NSABP 18 study analysis [3], patients who were not eligible for BC prior to NT fared worse in terms of local failure rates compared to patients who were eligible to BC upfront.

The extent of imaging required prior to embarking on an attempt at BC after NT is also a matter of controversy. Clearly, MRI could add information regarding the residual tumor extent, and we ordered it when possible; in 10/30 patients MRI was performed, and in 20/30 patients only a repeat mammography and ultrasound was performed.

In our series all patients underwent an operation with the goal of removing the entire tumor with negative margins. In addition, radiation therapy was mandated for all patients and was thus administered, except to one non-compliant patient and one nonagenarian. Only patients with tumor on the inked margins were recommended to have a re-excision. Size in centimeters was measured on presentation by imaging; all patients were downstaged for BC by NT and we had no cutoff size for BC. We can conclude that at a mean follow-up of 43 months, BC is a safe option for tumors

Table 3
Studies including BCT for T3 patients following neoadjuvant chemotherapy.

Authors	Trial	Follow-up months	BCT	T3	Selection criteria	Local failure	Distal failure
Touboul et al. (1997) [10]	Prospective	82	95	51 (53%)	Residual tumor <3 cm	20%	24%
Bonadonna et al. (1998) [11]	Prospective	96	455	52 (11%)	If tumor sufficiently reduced in size	4.3%[a]	–
Fisher et al. (1998) [3]	Prospective	60	450	96 (13%)[b]	Not specified	7.9%	–
Mauriac et al. (1999) [12]	Prospective	124	84	29 (22%)[b]	Residual tumor <2 cm	31%	45%
Rouzier et al. (2001) [13]	Retrospective	60	257	23 (10.1%)	Residual tumor <3 cm	16%	34.1%
Kuerer et al. (2001)[14]	Retrospective	53	109	27 (25%)	Not specified	5%	11%
Chen et al. (2004) [15]	Retrospective	60	340	83 (24%)	Not specified	5%	13%
Rouzier et al. (2004) [16]	Retrospective	60	287	52 (18%)	Residual tumor <3 cm	10%	25%
Mamounas et al. (2012) [17]	Prospective	120	1890	776 (25%)[b]	Not specified	10%	–
Libson et al. (2015)	Retrospective	43	30	30 (100%)[c]	Surgical feasibility	0	13.3%

[a] Failure rate for T3 patients alone.
[b] T3 rate included patients who underwent BC + mastectomy.
[c] Including 5 cm tumors.

≥5 cm downstaged by NT, when pathological margins are negative and radiation is administered.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

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